Amendments to the Specification

Please replace the paragraph beginning at page 1, line 1, with the following amended paragraph:

TITLE: Detection of Pathogenic Polypeptides using an Epitope Protection Assay ~~and Method for Detecting Protein Conformations~~

Please replace the paragraphs beginning at page 6, line 1 to page 7, line 20, with the following amended paragraphs:

Alzheimer's Disease

AD is a common dementing (disordered memory and cognition) neurodegenerative disease associated with brain accumulation of extracellular plaques composed predominantly of the Abeta (1–40), Abeta (1-42) and Abeta (1–43) peptides, all of which are proteolytic products of APP (reviewed in 4). In addition, neurofibrillary tangles, composed principally of abnormally phosphorylated tau protein (a neuronal microtubule-associated protein), accumulate intracellularly in dying neurons (4). Familial forms of AD can be caused by mutations in the APP gene, or in the presenilin 1 or 2 genes ~~(www.websiteformutations.com)~~, the protein products of which are implicated in the processing of APP to Abeta. Apolipoprotein E allelic variants also influence the age at onset of both sporadic and familial forms of AD (reviewed in 5). Abeta has been detected in the blood and CSF of AD patients and in normal controls (6). Abeta is also present in vascular and plaque amyloid filaments in trisomy 21 (Down's syndrome), hereditary cerebral hemorrhage with amyloidosis (HCHWA)-Dutch type, and normal brain aging (Mori, H et al. JBC (1992) 267: 17082-86). Tau and phosphorylated tau have been detected in the cerebral spinal fluid (CSF) of AD patients and patients with other neurological diseases (7; reviewed in 8).

Amyotrophic Lateral Sclerosis

ALS is a fatal neuromuscular disease, with an incidence of 1 in 1000 adults, presenting as progressive weakness, muscle atrophy, and spasticity, which is due to degeneration of ~500,000 "lower motor neurons" in the spinal cord and brainstem, and innumerable "upper motor neurons" in the brain cortex. An important clue to the etiology of ALS came with the finding that about 20% of familial ALS (fALS) cases are due to mutations in superoxide dismutase-1 (SOD1) (10,11), a free radical defense enzyme. Over 100 fALS SOD1 missense, nonsense, and intronic splice-disrupting mutations have been catalogued to date (12~~; www.alsod.org~~). Transgenic mice expressing mutant human SOD1 (mtHuSOD1) develop a motor neuron syndrome with clinical and pathological similarities to human ALS (13, 14), whereas mice expressing wild-type human SOD1 (wtHuSOD1) do not develop disease (13). SOD1-containing cytoplasmic inclusions can be detected in many diseased motor neurons from familial and sporadic ALS patients (15), and in most transgenic mouse (16, 17) and tissue culture (18) models of the disease.

Parkinson's and Lewy Body Disease

PD is a neurodegenerative movement disorder second only to AD in prevalence (~350 per 100,000 population; 1). It is clinically characterized by rigidity, slowness of movement, and tremor (reviewed in 21). Most cases of Parkinson's disease are sporadic, but both sporadic and familial forms of the disease are characterized by intracellular Lewy bodies in dying neurons of the substantia nigra, a population of midbrain neurons (~60,000) that are selectively decimated in PD. Lewy bodies are predominantly composed of alpha-synuclein (22). Mutations in the gene encoding alpha-synuclein have been found in patients with familial Parkinson's disease (reviewed in 23~~; www.parkinsonsmutation.com~~). Another gene associated with autosomal recessive PD is parkin, which is involved in alpha-synuclein degradation (22, 23). Diffuse cortical Lewy bodies composed of alpha-synuclein are observed in Lewy body disease (LBD), a dementing syndrome associated with parkinsonian tone changes, hallucinations, and rapid symptom fluctuation (24). LBD may be the second most common form of neurodegenerative dementia after AD, accounting for 20 to 30 percent of cases among persons over the age of 60 years (1, 24).